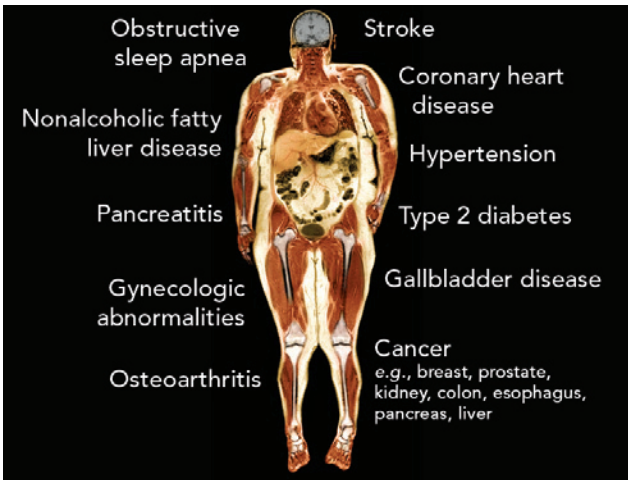
Obesity

Individuals who are obese may suffer devastating health problems, face reduced life expectancy, and experience stigma and discrimination. Obesity is a strong risk factor for type 2 diabetes, fatty liver disease, and many other diseases and disorders. A common, chronic, and costly condition, obesity affects more than one-third of adults in the U.S. and 16 percent of children—who are at risk for developing serious diseases both during their youth and later in adulthood.[2] Obesity also disproportionately affects racial and ethnic minority populations, and those who are socioeconomically disadvantaged. Thus, NIDDK supports a broad spectrum of obesity research to understand the factors that influence body weight, illuminate how obesity leads to disease, and develop and test prevention and treatment strategies in the clinic and community settings.

A CONVERGENCE OF BIOLOGY AND THE ENVIRONMENT

The Discovery of Leptin, and Molecular Regulation of Body Weight: The body's adipose tissue—or fat—sustains life in times of famine and fuels physical activity and vital biological processes, but too much fat is a recipe for metabolic disaster. Although scientists had recognized for decades that obesity, or excess fat, is linked to type 2 diabetes and other diseases, it wasn't clear why. However, there were hints that not all fat tissue is the same, and that the amount of body fat is regulated.

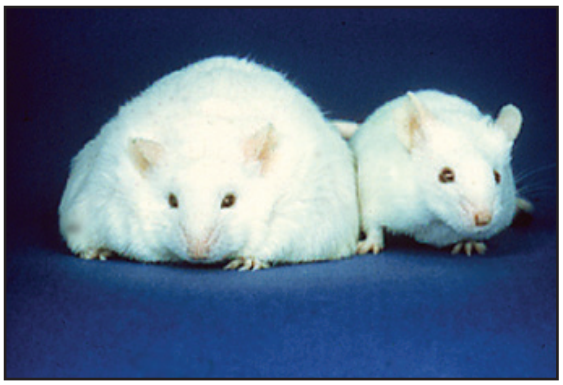
In 1994, NIDDK-supported scientists studying obese mice identified the gene for the hormone leptin—a discovery that would ignite an explosion of research into the control of appetite and body weight, shine a spotlight on the role of adipose tissue in regulating metabolism, and change perceptions about obesity. Subsequent research showed that leptin, which is produced by fat cells, travels to a key control center



Whole-body scan of an individual who is obese. Potential obesity-associated health complications are indicated.
Image credit: Adapted from image created by Dr. Wei Shen and Dr. Steven Heymsfield, New York Obesity Research Center, St. Luke's-Roosevelt Hospital, Columbia University, New York.

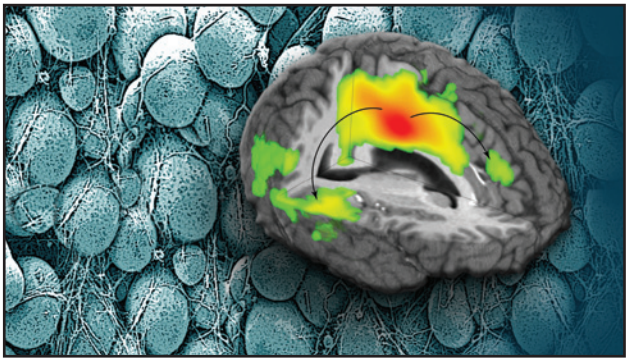
[2] *National Center for Health Statistics, CDC, Data Brief Number 1, 2007; and* JAMA *299: 2401-5, 2008. Obesity in adults is defined as a body mass index (BMI, a measure of weight relative to height) of 30 or greater. For children, this document uses the term obesity to refer to a BMI at or greater than the 95th percentile on growth charts (which are based on previous national surveys).*

in the brain to report on the body's energy stores and reduce appetite. For people who lack leptin due to very rare genetic mutations, administration of this hormone effectively treats their extreme obesity. Demonstrating a genetic and hormonal basis for excess body weight, this research also underscored that appetite control could no longer be viewed as solely a "willpower" issue. Most people who are obese do not have leptin deficiency, and in fact, have very high levels of leptin, but in obesity, the body appears to become resistant to this hormone's actions. Years of research have shown that genetic factors nevertheless strongly influence common forms of obesity as well. As many as 5 percent of individuals with early onset severe obesity may have a defect in a brain molecule known as the melanocortin-4 receptor. With advanced genome-wide analyses, scientists are identifying additional genes associated with common forms of obesity.



Mutation of the receptor for the hormone leptin causes obesity in the mouse on left, compared to a normal mouse on the right.
Image credit: Image courtesy of the Jackson Laboratory.

Since the discovery of leptin, NIDDK-funded researchers have elucidated an extraordinarily complex regulatory system of hormones and other molecular signals that not only sense the body's energy stores (in the form of fat) to modulate appetite and satiety, but also respond to the rewarding nature of tasty food. Signaling factors produced in the brain as well as those secreted by fat tissue and other parts of the body converge in the brain to regulate body weight. Just a few examples are the hormone ghrelin, which is released from the gut and acts on the brain to stimulate appetite; apo A-IV, which reduces food intake after a high-fat meal; and factors such as mTOR, serotonin, and others. Other research has advanced knowledge of the many biologic processes that contribute to regain of lost weight and body fat, including hormonal and other changes that affect hunger and energy expenditure (calorie burning). Very recently, neuroimaging studies revealed that the sight of food elicits different patterns of brain activity in obese people before and after weight loss; leptin administration reversed many of these changes. The exciting insights from these and other studies are providing potential targets for new drug development and may inform other treatment approaches with the goal of helping people lose excess body fat and maintain the weight loss long-term.



Neuroimaging, with such methods as a brain scan (foreground image) can reveal aspects of brain activity associated with obesity (represented by the fat cells in the background).
Image credit: Brain scan of cingulate functional connectivity, courtesy of Dr. Elliot Hong (Maryland Psychiatric Research Center), and Drs. Elliot Stein and Thomas Ross (National Institute on Drug Abuse).

"Brown" Fat Tissue: Not all body fat, or adipose tissue, is the same. White adipose tissue stores extra calories as fat for later use; obesity is an excess of this type of fat tissue. Another type of fat, "brown" adipose tissue, burns fat molecules to dissipate heat and helps keep babies and small animals warm. In humans, brown fat tissue was previously thought to disappear after infancy, but in 2009, NIDDK-supported scientists and other research teams discovered that brown fat is present in adult humans and appears metabolically active with exposure to cooler temperatures. They also found that people who are overweight or obese seem to have less active brown fat. NIDDK-funded scientists are also elucidating how brown fat cells develop, and have discovered that some brown fat arises from the same precursor cells as another energy-burning tissue—muscle—while other brown fat cells may share a lineage

with white adipose cells. These findings suggest a novel strategy for treating obesity: generating more brown fat cells to burn more excess calories.

Food, Physical Activity, and Fidgeting: Beyond the biologic factors within us, aspects of our environment can also contribute to obesity: the availability of healthy foods and beverages; opportunities for physical activity; and the pervasive lure, or necessity, of sedentary behaviors. In research on eating behaviors, for example, NIDDK-supported scientists have shown that larger portion sizes lead to greater food consumption. In the realm of activity, an NIDDK-funded study of thousands of women found that sedentary behavior, particularly sitting while watching television, is predictive of greater risk for obesity and type 2 diabetes. Another team of NIDDK-funded scientists discovered that among self-described "couch potatoes," people who are lean tend to stand and move far more than those who are obese. Fidgeting—technically "non-exercise activity thermogenesis"—may thus burn a substantial number of calories.

Gut Bacteria and Obesity: A surprising contributor to obesity may be the bacteria and other microbes that reside in the gut. NIDDK-funded scientists recently discovered that gut microbes differ between lean and obese individuals: microbes associated with obesity may be better at harvesting extra calories from food. Gut microbes also influence the body's storage of calories as fat. Manipulation of gut microbes may thus be a novel approach to prevent or treat obesity.

Linking Excess Fat to Disease: NIDDK-supported research on obesity has advanced understanding of how excess fat leads to disease. Earlier research had shown that fat in certain areas of the body confers heightened risk for type 2 diabetes, especially tissue now referred to as "visceral" fat, or fat around the organs deep within the abdomen. Within the past decade, scientists have identified molecular links between obesity and associated health problems. For example, a hormone produced in adipose tissue, adiponectin, helps the body respond to insulin. In obesity, abnormally low levels of adiponectin are associated with insulin resistance, which is a risk factor for and hallmark of type 2 diabetes. Scientists have also found that elevated levels of another factor, called RBP4, are associated with insulin resistance, as well as type 2 diabetes and cardiovascular disease risk, and thus may be a potential diagnostic marker and therapeutic target. RBP4 is produced by visceral fat cells. Several other factors secreted by adipose tissue promote chronic inflammation, which has been linked to type 2 diabetes and cardiovascular disease risk. In 2003, researchers made the surprising discovery that some of these factors, such as TNF-alpha, are produced by cells of the immune system, called macrophages, which infiltrate fat tissue. Levels of another hormone, resistin, also contribute to insulin resistance. Originally identified as a fat cell-derived factor in mice, resistin interestingly is secreted by macrophages in humans. In an emerging area of research, scientists are learning that the link between fat and disease can begin early in life. NIDDK intramural researchers have shown that maternal type 2 diabetes during pregnancy leads to increased risk for the offspring to develop diabetes and obesity later in life. Focusing on another disease, researchers studying non-human primates observed that maternal consumption of a high-fat (and high-calorie) diet during pregnancy—similar to a typical American diet—results in extensive fatty liver disease in the offspring. Although the mechanisms for these effects are not yet clear, they may involve epigenetics—molecular modifications that affect gene activity without changing the DNA sequence.

PREVENTION AND TREATMENT STRATEGIES

Lifestyle and Medical Interventions: The NIDDK has sponsored numerous studies of approaches to prevent or treat excess weight gain and lower risk for obesity-associated disease. For example, one recent study showed that a strategy to reduce television and computer use beneficially affects body mass index (BMI, a measure of weight relative to height) in young children, particularly those from a socioeconomically disadvantaged background. Other researchers found that an intervention to reduce consumption of sugar-sweetened beverages in teens had a beneficial effect on body weight in those who, at the beginning of the study, had very high body weights compared to

their peers. In a study with obese adults, researchers showed that treatment with a lifestyle modification program of diet, exercise, and behavioral therapy, when used in combination with the weight-loss medication sibutramine, resulted in significantly greater weight loss than treatment with the medication alone. Exploring the challenging task of maintaining weight loss, scientists leading the Study to Prevent Regain (STOP Regain) clinical trial discovered that a face-to-face intervention incorporating daily self-weighing can help adults maintain a desired weight following weight loss. Many other studies are ongoing to investigate a variety of approaches to prevent or manage overweight and obesity in children and adults, in diverse populations, and in a variety of settings, such as the home, school, and other community sites.

Lifestyle factors such as physical activity and healthy eating can help kids to avoid obesity and its complications.
Photo credit: Jupiterimages.

A major study focused on a disease associated with obesity, type 2 diabetes, was the Diabetes Prevention Program (DPP). This landmark clinical trial, which was conducted at sites throughout the country, demonstrated that people who are overweight or obese and at high risk for type 2 diabetes can dramatically reduce their chances of developing the disease through modest weight loss, achieved with moderate exercise and reduced dietary fat and calories. The lifestyle intervention, which was based on extensive prior behavioral research, worked in both men and women, and in all ages and racial and ethnic groups studied. The DPP results were announced in 2002, and a follow-up study has recently shown that the health benefits have continued. (See additional information in the Diabetes, Endocrinology, and Metabolic Diseases chapter.)

Another large clinical trial, Look AHEAD (Action for Health in Diabetes), is focused on overweight and obese adults who already have type 2 diabetes. Currently ongoing at research centers around the country, Look AHEAD is examining the health effects of a lifestyle intervention designed to achieve and maintain weight loss over the long term, through exercise and decreased caloric intake. The study will assess the impact of the intensive lifestyle intervention on the incidence of heart attack, stroke, and cardiovascular-related death, along with other outcomes. Over 5,000 participants have enrolled, including both men and women, and members of minority groups disproportionately affected by obesity and diabetes. Encouraging results from the first year of the trial, reported in 2007, showed that clinically significant weight loss could be achieved through the lifestyle intervention, and led to improvements in health-related quality of life, cardiovascular fitness, blood pressure, cholesterol, and blood glucose. These results are particularly important in light of the fact that previous research had suggested that weight loss and maintenance might be more difficult in obese individuals with type 2 diabetes.

The Program to Reduce Incontinence by Diet and Exercise (PRIDE) study demonstrated another health benefit of weight loss. In 2009, researchers reported that women who are overweight or obese can significantly reduce their episodes of urinary incontinence through modest weight loss.

Surgical Treatment for Extreme Obesity: For people who are extremely obese, bariatric surgical procedures are being increasingly performed and can have dramatic health benefits, such as improved control of blood sugar or even reversal of type 2 diabetes, but also carry serious health risks. Thus, the NIDDK supports a multi-center observational study, the Longitudinal Assessment of Bariatric Surgery (LABS), to advance understanding of the risks and benefits of these procedures. Recently, LABS researchers found that short-term complications and death rates were low following bariatric surgery; the study is continuing to assess longer-term outcomes. The NIDDK is additionally supporting the Teen-LABS observational study to evaluate the surgery's risks and benefits in

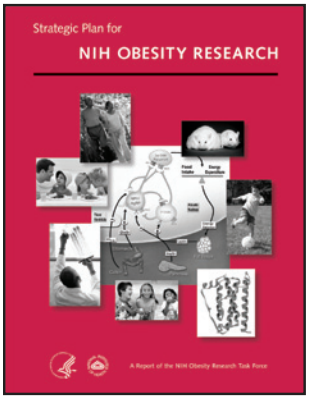
adolescents. (Additional information is presented in the Digestive Diseases and Nutrition chapter.)

EDUCATION AND OUTREACH PROGRAMS

Information from NIDDK's Weight-control Information Network.

In addition to funding basic and clinical research, the NIDDK also sponsors educational and outreach programs to disseminate science-based information. The Institute established the Weight-control Information Network (WIN) in 1994 to provide the general public and health professionals with up-to-date, science-based information on obesity, weight control, physical activity, and related nutritional issues (http://win.niddk.nih.gov/index.htm). Among WIN's many publications is a series of booklets, in English and Spanish, on "Healthy Eating and Activity Across Your Lifespan." WIN also developed a national initiative, *Sisters Together: Move More, Eat Better*, to encourage Black women to maintain a healthy weight by becoming more physically active and eating healthier foods. A recently-published WIN brochure is designed to help men get fit and lose weight. The NIDDK also co-sponsors *We Can!* (Ways to Enhance Children's Activity and Nutrition), a national education program led by the National Heart, Lung, and Blood Institute. *We Can!* is designed for families and communities to help children 8-13 years old maintain a healthy weight (http://wecan.nhlbi.nih.gov).

LOOKING TO THE FUTURE



Strategic Plan for NIH Obesity Research U.S. Department of Health and Human Services, National Institutes of Health, August 2004, NIH Publication No. 04-5493.

Building on the discoveries and opportunities emanating from past research, the NIDDK—and the scientists it supports—will continue to pursue new insights into the complex problem of obesity, develop and test prevention and treatment strategies, and expand the scientific evidence base that can be used to inform policy making and other community efforts. These multidimensional research efforts will continue to be informed by input from external scientists and clinicians at universities and other institutions and members of the broader public through the NIDDK Clinical Obesity Research Panel, scientific workshops, and other venues. Additionally, the Institute has a leadership role on the NIH Obesity Research Task Force, which in 2004 developed a *Strategic Plan for NIH Obesity Research* with extensive external input. The Task Force is currently updating this *Plan*. Through continued advances in obesity research, the NIDDK aims to improve people's lives and public health.

Photo credit: Getty Images.